UNITED STATES PATENT AND TRADEMARK OFFICE

C1C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,856	03/21/2002	Andrew Austen Mortlock	Z70598-1	6741

44992 7590 10/21/2005

ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,856	MORTLOCK ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7-27-05 (RCE)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,10-13,18,21-27,29 and 31-37* is/are pending in the application.

4a) Of the above claim(s) *23,24,26,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,10-13,18,21,22,25,27,29,31-33,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-27-05 has been entered.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group 1: Claims 1, 6, 7, 10-13, 21, 22, 25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (i) or (ii);

R^{80} is sub-formula (II);

classified in classes 514 and 544, various subclasses depending on substituents . Election of species will be required if this group is elected.

Group 2: Claims 1, 6, 7, 10-13, 23-25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (i) or (ii);

R^{80} is sub-formula (d);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 3: Claims 1, 6, 7, 10-13, 25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (i) or (ii);

R^{80} is formula (VI);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 4: Claims 1, 6, 7, 10-13, 25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (i) or (ii);

R^{80} is sub-formula (f);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 5: Claims 1, 6, 7, 10-13, 18, 21, 22, 25, 27, 29, 31-33, 36 and 37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iii) or (v);

R^{80} is sub-formula (II);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 6: Claims 1, 6, 7, 10-13, 18, 23-25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iii) or (v);

R^{80} is sub-formula (d);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 7: Claims 1, 6, 7, 10-13, 18, 25, 27, 29, and 31-37 (part of each),

drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iii) or (v);

R^{80} is formula (VI);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 8: Claims 1, 6, 7, 10-13, 18, 25, 27, 29, and 31-37 (part of each),

drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iii) or (v);

R^{80} is sub-formula (f);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 9: Claims 1, 6, 7, 10-13, 21, 22, 25, 27, 29, and 31-37 (part of each),

drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iv);

R^{80} is sub-formula (II);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 10: Claims 1, 6, 7, 10-13, 23-25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iv);

R^{80} is sub-formula (d);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 11: Claims 1, 6, 7, 10-13, 25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iv);

R^{80} is formula (VI);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 12: Claims 1, 6, 7, 10-13, 25, 27, 29, and 31-37 (part of each), drawn to compounds of formula I with the following substituents:

R^5 is sub-formula (iv);

R^{80} is sub-formula (f);

classified in classes 514 and 544, various subclasses depending on substituents.

Election of species will be required if this group is elected.

Group 13: Claim 26, drawn to a compound of formula VII which is an intermediate,

Classified in class 544, various subclasses depending on substituents. Election of species will be required if this group is elected.

Inventions of Group 1 - 13 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to compounds of different combinations of rings and substituents.

The compound of one group differs from the others by the rings represented by R^5, and its substituent R^{80}. Although all 13 groups share the *quinazoline* core, such a core does not sufficiently define the invention, or contribute to the art. Thus, it is the combination of *quinazoline*, X, R^5-R^{80} that gives the unique physical and chemical properties to the compound in each group. For that reason, a reference that anticipated or rendered obvious compounds of one group would not do so to those of the other groups. Therefore, a separate search and examination are required for each group.

Note, the broad on-line search yields 1240 hits in STN Registry File while the search of the *quinazoline-(R^5= pyrimidine)* group alone yields 619 hits on EAST. Such a volume of references proves a serious burden of searching.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art due to their recognized divergent subject matter, and to search the 13 distinct inventions would indeed impose a serious burden upon the examiner in charge of this invention, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Lucy Padget on 9-29-05 a provisional election was made with traverse to prosecute the invention of Group 5, claims 1, 6, 7, 10-13, 18, 21, 22, 25, 27, 29, 31-33, 36, and 37 (part of each) . Affirmation of this election must be made by applicant in replying to this Office action. Note, Group 5 has been revised to exclude claim 34 (wherein R^5 is formula (i)), and claim 35 which depends on the non-elected claim 24.

Claims 23, 24, 26, 34 and 35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 6, 7, 10-13, 18, 21, 22, 25, 27, 29, 31-33, 36, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 1 recites the limitation of "*prodrug*", which had indefinite metes and bounds because it is not clear where the functional group for a "*prodrug*" would be. Also, many of the substituents are amide, sulfonamide, alkoxycarbonyl, etc., thus, it is not clear if a compound having such a substituent would be considered a "*prodrug*".

b. Claim 1 recites the phrase "*any aryl, heteroaryl or heterocyclyl group in a substituent on* R^5" in the middle of the definition of R^{70}, which makes it unclear if R^5 optionally has additional substituents or if R^{70} optionally has additional substituents.

c. Claim 1 also recites many limitations in parentheses, which is unclear if they are part of the claim, or a mere explanation.

d. Claim 6 lacks antecedent basis because it depends on claim 1, but recites the limitation of "NR^7R^8" for R^1-R^4, which is not recited in claim 1.

e. Claim 10 recites the phrase of "R^9 *includes a methylene group...*", which is unclear as to which group in claim 1 is intended for R^9 since many of the groups could have a "*methylene*" group.

f. Claim 11 lacks antecedent basis because it depends on claim 1, but recites X^1R^9 "*which includes a bridging alkylene,...*", which is not recited in claim 1.

g. Claims 7, 12, 13, 18, 21, 22, 25, 27, 29, 31-33, 36, and 37 are rejected as being dependent on claim 1, carrying over the indefinite limitations.

Claim Rejections - 35 USC § 112, First Paragarph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Lack Written Description:** Claims 1, 25, 27, 29, 36, and 37 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "prodrug" in said claims does not have adequate written description. On page 22, the specification briefly describes "prodrugs" as "*groups which enhance solubility and include phosphates and sulphates. The prodrug moiety may be attached at any suitable position in the molecule..., and preferably at R^2 or R^3.* " However, the specification does not teach how such a phosphate or sulfphate group can be added to the particular position. Thus, the limitation of "prodrug" lacks a written description. As mentioned in the 112/2nd rejection above, many substituents of R^1-R^4 have ester, amide, sulfonyl groups, would they also be considered a functional group of a "prodrug"?

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **Scope of Enablement:** Claims 27 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating colorectal or breast cancer, does not reasonably provide enablement for a method of treating "*hyperproliferative disease*", or cancer in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 27 recites: "A method for treating hyperproliferative disease..." which covers many untreatable cancers such as: liver cancer, pancreatic cancer, etc., and non-cancerous

diseases such as psoriasis, angiogenesis as well as embryogenesis (though not a disease, but sill involves rapid cell growth).

Claim 36 recites: "A method for treating cancer..." which covers numerous cancers of different organs, and tissues.

Both claims 27 and 36 refer to a large number of quinazoline compounds, and thus, their scopes are not only broad in term of possible diseases to be treated, but also in term of a large genus of compounds.

The amount of direction or guidance presented:

The specification only provides *in-vitro* assay of the inhibition of aurora2 kinase which allegedly could inhibit cell cycle, and cell proliferation. However, only compound #6 is tested for such activity. Considering a large genus such as the instant formula (I), the activity of one compound cannot be extrapolated to the entire genus since the extensive substitution on the quinazoline ring could hinder such activity. Furthermore, from the *in-vitro* cell proliferation assay, it is not conclusive whether the claimed compounds could treat any disease. For one thing, inhibiting cell proliferation essentially stops the growth of all cell types, and not just cancerous cells. Thus, a mere showing of *in-vitro* activity does not sufficiently guide the skilled clinician to practice the claimed method in an effective and safe manner.

The state of the prior art:

As evident by the teaching of **Unckun et. al.** (US 6,258,820), an analogous set of quinazoline compounds can be used to treat leukemia. However, the disclosed genus is not as extensively substituted as the one claimed herein, and covers a limited number of compounds.

Likewise, the teaching of **Myers et. al.** (US 5,721,237) discloses a genus of quinazoline compounds that can inhibit HER2 receptor, which is known to treat colorectal and breast cancers. Therefore, at most, following those two teachings, the skilled clinician could only use a few compounds of the instant formula I in the treatment of leukemia, colorectal and breast cancers.

The relative skill of those in the art:

Even with the advanced training (e.g., PhD. or MD program), the skilled clinician would have to engage in undue experimentation to select any of the claimed compounds and use it to treat a cancer or any disease that is not taught by state of the art. For each compound beyond the scope of Uckun et. al. or Myers et. al., the skilled clinician would have to determine a therapeutic index, and a pharmacokinetic profile which would be effective and safe to treat any disease other than leukemia, colorectal and breast cancers. Such a task is not routine experimentation, and would require a tremendous amount of effort, time and resources.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. Besides, the *in-vitro* activity of one compound does not warrant *in-vivo* activity. Thus, with the limited guidance provided by the specification and state of the art, the skilled clinician would have to carry out undue experimentation to apply a large number of compounds claimed herein in the

treatment of "*hyperproliferative disease*" or cancer in general as recited in the instant claims 27 and 36.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1, 6, 7, 10, 12, 13, 18, 21, 27, 29, 31, 33, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Myers et. al.** (US 5,721,237).

On column 3, Myers et. al. disclose a quinazoline genus of formula I which generically encompasses compounds of the instant formula I with the following substituents:

i. Any one of R^1-R^4 is X^1R^9 wherein X^1 is –O- and R^9 is an alkyl group, which corresponds to the reference's R^5-R^8 as an alkoxy group.

ii. X is O, S, S(O), $S(O)_2$, or NR^8 which corresponds the reference's X variable.

iii. R^5 is formula (iii) or (v), which corresponds to the reference's ring A as a pyrimidinyl (see the definition of "Monocyclic aryl" on column 3, lines 45-50).

iv. R^{80} is formula II wherein s' = 0; q' = 0; R^{99} is hydrogen; X^{12} is C(O), and R^{70} is hydrogen. Note, formula II corresponds to "*acylamino*", or "*amido*" group represented by the reference's variable R, which is a substituent on ring A.

The disclosed genus can inhibit HER2 receptor, which is known to treat leukemia, colorectal and breast cancers. Thus, the method of treatment and pharmaceutical composition recited in the instant claims 27, 29,36 and 37 are also rendered obvious by the activity of the disclosed genus.

The teaching of Myers et. al. differs from the instant claims by not disclosing a species having "*acylamino*", or "*amido*" on ring A. However, the disclosed genus only had presented a limited number of compounds from which a skilled chemist could have selected and expected reasonable success. Therefore, at the time that the invention was made, it would have been obvious for the skilled chemist to make compounds of the instant formula I, and use them in the treatment of colorectal and breast cancers in view of the teaching above.

No pending claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***

10-14-05

Tamthom N. Truong
Examiner
Art Unit 1624

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600